Autoimmune hypophysitis: a single centre experience

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ABSTRACT

Introduction: Autoimmune hypophysitis (AH) is a rare primary autoimmune inflammatory disorder involving the pituitary gland.

Methods: A retrospective analysis of the clinical features and outcome of patients diagnosed with AH between 1988 and 2006, was carried out.

Results: 15 patients (14 females and one male) with AH were identified. Three patients presented in the peripartum period. Headache, vomiting and visual field defects, suggestive of an expanding sellar mass, were the most common presenting symptoms (67 percent). The most common deficient hormone was adrenocorticotropic hormone (ACTH) (67 percent), followed by thyroid stimulating hormone (53 percent) and gonadotropins (40 percent). Imaging revealed a definite, enhancing sellar mass in 87 percent of the patients and stalk thickening in 33 percent of the patients. Three patients underwent surgery. On serial monitoring, the sellar mass regressed or disappeared spontaneously without any immunosuppressive treatment in the other ten patients with a definite sellar mass.

Conclusion: We report a higher female to male ratio and a lower incidence of peripartum cases in our series. Symptoms of mass effect were the most common presentation, while ACTH was the most commonly-deficient hormone. Surgery was rarely needed, and most patients experienced a spontaneous resolution of the mass.

Keywords: autoimmune hypophysitis, hypopituitarism, pituitary gland, sellar mass

Singapore Med J 2009;50(11):1080-1084

INTRODUCTION

Autoimmune hypophysitis (AH) is a rare primary autoimmune inflammatory disorder involving the pituitary gland. Since the first description by Goudie and Pinkerton in 1962,[1] about 400 cases have been reported to date. The estimated incidence of AH is one in nine million per year.[2] It occurs predominantly in young females, especially in the peripartum period.[3] The classical presentation is symptoms of sellar mass with or without varying degrees of hypopituitarism. The patients may have evidence of other associated autoimmune diseases.[4] Histopathology is required for a definitive diagnosis, but many cases have been managed solely on clinical grounds.[3] The natural history of this disease, which ranges from spontaneous recovery to death due to unrecognised hypocortisolism, is still elusive. To add to the scant but valuable information regarding AH, we present our experience with this disease.

METHODS

The endocrinology department clinical register from a tertiary care centre in western India was searched for cases of AH diagnosed between 1988 and 2006. The diagnosis of AH was based on the following criteria: histopathologically-proven cases, and preferential involvement of the adrenocorticotropic hormone (ACTH) and thyroid stimulating hormone (TSH) over that of gonadotropins, typical imaging findings and/or the presence of associated autoimmune diseases in nonoperated cases.

A retrospective analysis of the clinical features and outcome of the patients was done. Hormonal deficiencies were defined and diagnosed as per our hospital protocol. Secondary hypocortisolism was defined as basal cortisol < 5 μg/dL. If basal cortisol was 5–10 μg/dL, a 250-μg synacthen test was performed; and a stimulated cortisol of ≥ 18 μg/dL was considered sufficient to define normocortisolaemia. Central hypothyroidism was defined as total thyroxine < 4.5 ng/ml with TSH < 20 μIU/ml. Patients were considered to have secondary hypogonadism if the follicular stimulating hormone and leutinising hormone were each less than 2.5 mIU/ml in women with amenorrhoea and in men with low-serum testosterone (< 4.0 ng/ml). Patients with a serum prolactin level > 25 ng/ml were considered to have hyperprolactinaemia, while those with < 5 ng/ml were considered to have hypoprolactinaemia.

RESULTS

15 patients (14 females and one male) with AH were identified, of which the first three cases had been previously reported.[5] All the female patients were in the reproductive

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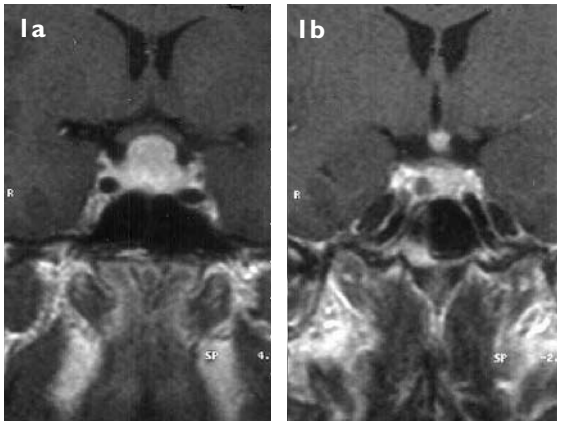

Fig. 1 MR image of the pituitary of Case 9 shows a large sellar mass with supra sellar extension with (a) intense homogenous post-contrast enhancement, and (b) stalk thickening.

age group except for two postmenopausal women. Three patients presented in the peripartum (two antenatal and one postpartum) period. The mean age of the female patients at the time of presentation was 36.5 years, while the male patient was 43 years of age. The clinical presentation in two-thirds of the patients was headache, vomiting and visual field defects (VFD), suggestive of an expanding sellar mass, including pituitary apoplexy-like presentation in two patients (Cases 7 and 13). Both cases presented with a sudden onset headache and extraocular muscle involvement. The remaining five patients presented with features of anterior pituitary hormone deficiencies. One patient with an apoplexy-like presentation had transient diabetes insipidus (DI) which lasted for one month, while none presented with galactorrhoea.

All except two patients had features of hypopituitarism (86.7%). ACTH was the most commonly-deficient hormone (67%), followed by TSH (53%) and gonadotropins (40%). Two patients had hyperprolactinaemia (both associated with pregnancy), while two had hypoprolactinaemia, of which one had lactational failure. One patient had transient DI. A routine evaluation of growth hormone status was not done. Associated autoimmune disorders were present in two patients. One patient had Sjögren's syndrome with distal renal tubular acidosis, rheumatoid arthritis and vitiligo, while another patient had autoimmune thyroiditis.

Imaging was done in all the patients using computed tomography or magnetic resonance imaging. A definite, enhancing sellar mass 1–1.7 cm in size was seen in all except two patients, one of the whom had a mild enlargement of the pituitary with stalk thickening, while the other had only stalk thickening. Stalk thickening was also present in three other patients with definite sellar mass. The imaging findings of Case 9 at the time of presentation are shown in Fig. 1. Autoimmune infiltration with lymphocytes and plasma cells with occasional lymphoid follicles were

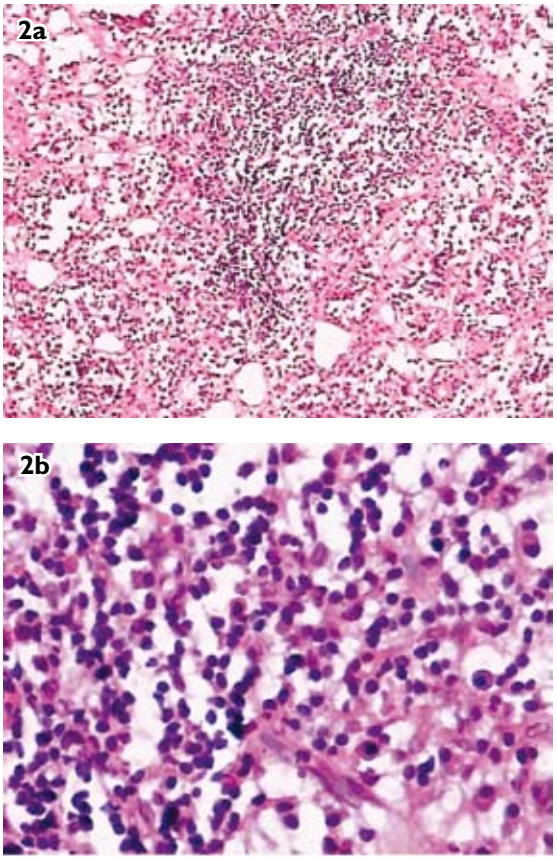

Fig. 2 Photomicrographs of Case 7 show adenohypophysis that is densely infiltrated with lymphocytes (Haematoxylin & eosin, [a] × 10, [b] × 40).

demonstrated in the histopathology of all three patients who underwent transsphenoidal surgery (TSS). There was no evidence of involvement of the posterior pituitary. The histopathological findings of Case 7 are shown in Fig. 2.

Three operated cases were confirmed to have AH on histopathology, while diagnosis in the other cases was based on clinical presentations and imaging findings. The relevant clinical findings of the patients are given in Table I. The anti-pituitary antibody status was not assessed in any of the patients. Three patients underwent TSS, as two of them were unwilling to undergo observation, and the other had progressive vision loss, leading to monoocular blindness. Postoperatively, there was recovery of the thyroid axis in one patient while the other preoperative hormonal deficits continued in all three. All nonoperated cases were managed conservatively with replacement of deficient hormones. Repeat imaging was performed periodically (usually 6–12 monthly) along with evaluation of the hormonal axes. None of the patients received immunosuppressive therapy, as a part of the department protocol was based on the experience of the initial cases.[5]

Apart from the three cases that underwent TSS, the mass disappeared or regressed in the remaining ten cases that had definite sellar mass. One patient developed empty

Table I. Clinical features, hormonal abnormalities, imaging findings and course of patients with lymphocytic hypophysistis.

Case no.	Gender /age (years)	Clinical manifestations	Deficient hormones	Size of sellar mass (mm); stalk thickening	Duration of disappearance of mass (month); axes recovered	Special features
1	F/53	Headache, vomiting, lethargy, VFD	ACTH, TSH	11 × 8 × 8; no	24; none	Postmenopausal, VFD improved
2	F/40	Vomiting, diarrhoea, generalised weakness, amenorrhoea	ACTH, TSH, GON	14 × 13 × 13; no	43; none	
3	F/32	Headache, vomiting worsened with labour, VFD, peripartum period	–	17 × 14 × 12; no	14; none HyperP recovered	HyperP, VFD improved
4	F/47	Headache, lethargy, cold intolerance, VFD	TSH, GON	15 × 5; no	23; none	Sjögren's syndrome RA, distal RTA
5	F/30	Headache, vomiting, malaise	ACTH, TSH	MD 12; no	Operated; thyroid	
6	M/43	Headache, nausea	NIL	MD 12; no	3; none	AITD, low uptake toxicosis
7	F/42	Sudden onset headache, diplopia Rt 3rd, Lt 3rd, 4th and 5th CNP	ACTH, TSH	16 × 17 × 17; yes	23; adrenal	Apoplexy
8	F/24	Headache, peripartum	–	12 × 14 × 15; no	Operated	HyperP, conceived after surgery
9	F/61	Weakness, anorexia	TSH, GON, prolactin	14 × 12 × 9; yes	18	Postmenopausal, hypoP, empty sella on FU
10	F/32	Amenorrhoea, weight gain	ACTH, TSH, GON	16 × 14; no	12; thyroid	
11	F/36	Headache,	ACTH	MD 16; no	4; adrenal	Compression of chiasma
12	F/35	Headache, vomiting	ACTH	9 × 8 × 9; yes	3; none	
13	F/24	Sudden onset headache, generalised weakness, transient DI, BL 6th and Rt 3rd CNP peripartum	ACTH, GON, prolactin	16 × 17 × 13; yes	7; none	Apoplexy, central necrotic area +, Rt cavernous sinus extension, hypoP, lactational failure
14	F/22	Oligomenorrhoea, primary infertility	ACTH, GON	No mass; yes	No mass at presentation; adrenal	
15	F/35	Amenorrhoea, monocular blindness	ACTH, TSH	14 × 12 × 10; no	Operated; none	No improvement in vision

ACTH: adrenocorticotrophic hormone; AITD: autoimmune thyroid disease; F: female; FU: follow-up; Gon: gonadotropins; Lt: left; M: male; MD: maximum diameter; Rt: right; TSH: thyroid stimulating hormone; VFD: visual field defect; P: prolactinaemia; DI: diabetes insipidus; RTA: renal tubular acidosis; RA: rheumatoid arthritis; BL: bilateral; CNP: cranial nerve palsy

sella. The duration of the disappearance of the mass varied from three months to four years. Stalk thickening in the two patients without a definite pituitary mass did not disappear until their last follow-up at two and three years, respectively. The resolution or regression of the pituitary masses and/or deficiencies later confirmed the diagnosis. Spontaneous reversal of at least one endocrine abnormality was seen in five patients. Hypocortisolism was resolved in three patients, while hypothyroidism and hyperprolactinaemia were each resolved in one patient. Hyperprolactinaemia in the other patient was mild and clinically silent, not warranting treatment at the last follow-up. Both patients with extraocular muscle involvement had complete recovery of the ocular movements, while VFD was resolved in two of four patients.

DISCUSSION

AH is predominantly a disease of young females, with a reported female to male ratio of 5–6:1.[4,6] The female to male ratio in our series was 14:1, which was approximately twice that of previous reports. The mean age of presentation of females in our series was 36.5 years, similar to the reported mean age of 35 years.[4] Males tend to present later at 45 years of age, as seen in our only male patient, who presented at the age of 43 years. The association of AH with pregnancy is well recognised. Nearly 60% of cases in females were reported during the peripartum period, with the majority of patients presenting in the last trimester and in the first two months after delivery.[4] In our series, peripartum presentation occurred in only 21.4% of our female patients.

In our series, 66.7% of patients presented with headaches and visual disturbances, consistent with earlier reports.[4,6] Beressi et al reported visual disturbances in 40% of the cases with predominant optic nerve involvement rather than extraocular muscle involvement.[7] Similarly, visual disturbances were present in 40% of our patients, with VFD in three patients, extraocular muscle involvement in two patients and optic nerve involvement in one patient. Partial or

complete deficit of the anterior pituitary hormones was present in 86.5% of our patients, which is similar to the reported rate of 66%–97%.[8,9] The most commonly-deficient hormone in our series was ACTH (67%), similar to that reported by Beressi et al (60%–65%).[7] Isolated ACTH deficiency was seen in three of our patients, and such cases have also been previously reported.[10] TSH (53%) and gonadotropins (40%) were respectively the second and third most commonly-deficient hormones, and this observation was similar to that of Hashimoto et al's findings (47% and 42.2%, respectively).[11] Routine evaluation of the growth hormone status was not done, as its secretion is the least affected in AH.[4] This fact distinguishes AH from Sheehan's syndrome and nonfunctioning pituitary adenoma. Elevated prolactin has been reported in 16%–38% of patients with AH.[12,13] Hyperprolactinaemia was seen in two of our patients (13.3%), and both of them had presented during the peripartum period. Hypoprolactinaemia has also been previously reported with AH,[14] and two of our patients also had hypoprolactinaemia, one of whom had lactational failure.

Although the association of a normal pituitary function with AH is unusual,[15] our male patient had normal pituitary function. DI is associated with AH in 14%–20% of cases.[6,8,11] We had only one patient with transient DI associated with the apoplectic phase of presentation, which was likely due to the oedema associated with the apoplexy. Apoplectic presentation was seen in two patients (Cases 8 and 13), who presented with sudden onset headache and extraocular palsies. Both cases had intensely enhancing pituitary masses with stalk thickening, characteristic of AH. Case 13 also had central necrosis within the lesion. Case 8 had recovery of the adrenal axis along with regression of the mass, which differentiated the condition from pituitary adenoma. An apoplexy-like presentation is rare in AH but has been reported in the literature.[16,17] Both cases were managed conservatively and had regression of the mass with recovery of the extraocular movements.

Similar to earlier reports, a sellar mass was present in 86.7% of our cases.[5,8,9,13] Homogenous symmetrical enlargement of the pituitary gland, a thickened non-deviated stalk,[18,19] and a prompt, intense and homogenous enhancement of the mass after gadolinium contrast were the characteristic findings on MR imaging. Though less specific for AH, it can distinguish AH from pituitary adenomas. All our patients had homogenous enlargement of the pituitary with intense postcontrast enhancement. Stalk thickening was present in 33% of our patients, with the thickened stalk as the sole imaging finding in one patient. In a recent series, Gutenberg et al reported stalk thickening in 79% of the cases.[12] Some cases of AH may develop empty sella during the course of the disease, and this was observed in one of our patients.

Associated autoimmune diseases are seen in 18%–50% of cases of AH.[6,8] The most commonly-associated disease is autoimmune thyroid disease (15%–25%), while concurrent autoimmune adrenalitis, pernicious anaemia, insulin-dependent diabetes mellitus, vitiligo, autoimmune parathyroiditis, autoimmune polyglandular syndrome type 2, rheumatoid arthritis, celiac disease, systemic lupus erythematosis, Sjögren's syndrome and primary biliary cirrhosis are rarely reported.[6-8,20,21] The association of autoimmune disease in our series was 13.3%, including one patient with concurrent Hashimoto's thyroiditis, and another with Sjögren's syndrome, rheumatoid arthritis and vitiligo. Histopathology is the gold standard for diagnosis of AH.[15] The most characteristic finding is the infiltration of the pituitary with lymphocytes, along with plasma cells and macrophages around the atrophic acini of the pituitary cells. At times the lymphocytes form follicles with a germinal centre.[15] In our series, all three operated cases showed lymphocytic infiltration with occasional follicles, and plasma cells were also present in one patient.

Apart from the three cases which underwent surgery, the other cases were managed conservatively with replacement of the deficient hormones. While on follow-up, it was noted that the pituitary mass of all ten patients who had a definite sellar mass on imaging, had disappeared or regressed in size. None of them were treated with a supraphysiological dose of steroids or with any immunosuppressant drugs. Spontaneous resolution is the usual course, but this may not always be associated with a reversal of endocrine abnormality.[3,8] Only 50% of the patients with regression of the mass had recovery of at least one endocrine deficit. TSS is indicated only when the symptoms of sellar compression are serious and progressive, especially while on medical treatment or when high-dose corticosteroids are not tolerated. In our series, there was recovery of a single endocrine axis in one of the three patients who underwent surgery. Even though surgery is very effective in resolving the symptoms of suprasellar extension, its role in the improvement of preexisting endocrine deficits is not very impressive.[4]

In conclusion, we report a higher female to male ratio and a lower incidence of peripartum cases in our series. Symptoms of mass effect were the most common presentation, while ACTH was the most commonly-deficient hormone. Surgery was rarely needed, and most patients had spontaneous resolution of the mass.

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